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CHILDREN'S HOSPITAL

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CLINICAL PROCEEDINGS OF THE CHILDREN'S HOSPITAL

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Occasionally, the remarks and observations of guest speakers are included in this bulletin when thought to have particular interest. The proximity of the Children's Hospital to the Medical Centers of the Army, Navy and United States Public Health Service affords us the opportunity to invite many distinguished physicians to our conferences.

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ERRATA

Due to an error of the printer this issue is incorrectly folioed and should read pages 1–24.

MALIGNANT HYPERTENSION ASSOCIATED WITH UNILATERAL RENAL ATROPHY

Case Report No. 79

Dr. Frank Zinzi J. F.

An eight year old white female was brought to the hospital because of severe headache and a convulsion. The onset of this child's illness began three years prior to admission with headaches recurring with progressive intensity and frequency, sometimes accompanied by vomiting, unrelated to food. The headache and vomiting episodes would last for several hours before subsiding. Palliative medication had no beneficial effect during these attacks. Headache, as a symptom, did not seem to have any relationship to infectious disease, anemia, nervous causes, eyestrain, disorders of the upper respiratory tract or allergy. Efforts directed toward determining the etiology of this symptom complex had included radiographic studies of the skull, gastro-intestinal and genito-urinary tracts. The latter examination had revealed an enlarged left kidney and ureteroscopic investigation was performed. These procedures led to an appendectomy which was done in a local hospital two days prior to admission here. Twenty-four hours post-operatively the patient had her first convulsion which was described as predominately left sided and of four hours duration. Subsequently there had been a total of five similar convulsions, complicated by a sudden loss of vision. The inability to see was a presenting symptom at the time of transfer to the Children's Hospital.

The past history from birth to five years was not remarkable. Birth had been at term although the mother had been said to have hypertension in the second trimester of pregnancy. The delivery had involved no difficulties and the neonatal period was uneventful. Physical growth and development were ascertained to be normal during infancy and childhood. Uncomplicated pertussis was acquired at 3 months and German measles at 3 years. There had been no unexplained fevers.

Family history was non-contributory. Both parents were alive and in good health. Tuberculosis, syphilis, epilepsy, insanity, dystrophies or allergic manifestations—namely eczema or food idiosyncrasies or conditions similar to the disease of the patient—were denied.

On admission the temperature was 100°F., the pulse rate 100 and the respirations 25.

Physical examination revealed a well developed, poorly nourished white female, appearing somewhat underweight, acutely and chronically ill, constantly complaining of abdominal pain and inability to see.

Fundoscopic examination revealed a moderate papilledema of two diopters bilaterally. Flame shaped hemorrhages were present and the veins were distended. The arteries showed increased tortuosity with some fragmentation, but no cotton ball exudates were noted. The heart had an apical grade 1 soft blowing systolic murmur which was not transmitted. The cardiac sounds were of good quality and regular and there was no obvious enlargement by percussion or visible P.M.I. The blood pressure was 190/165 in the right arm, 185/160 in the left arm. In the right leg it was 220/170 and in the left leg 215/170. The abdomen revealed only some fullness in the right paraumbilical area and a clean healing incision, the result of her recent appendectomy.

Frequent urine analyses for a period of six weeks revealed a persistent cloudiness, a constant acid reaction, a constant specific gravity of 1.005 to 1.010, a spillage of albumin ranging between 5 and 200 mgm. and a few white blood cells. At no time were red blood cells, variable casts or bacteria found.

N.P.N. was 24 mgm.% and blood urea nitrogen 13.3 mgm.%. After the intravenous injection of 1 cc. of phenolsulphonphthalein and the ingestion of two glasses of water, 55% of the dye was excreted in the urine by the left kidney in 15 minutes and 35% in 30 minutes, a total of 90%. Excretion from the right kidney was not detectable.

A flat x-ray plate of the abdomen revealed no definite evidence of abnormality of the genito-urinary tract. The kidney shadows, however, could not be outlined because of gas in the bowel. Examination of the GU tract by the intravenous method revealed at the end of 4 minutes some clumps of dye in the left kidney region, and the upper half of the left ureter was visualized. At the end of 10, 20 and 30 minutes there was only a small amount of dye visualized in the right kidney and what was seen did not present the normal architecture. On the left side, however, the kidney was fairly well outlined, the calices and pelvis being somewhat dilated and cupped. The ureteropelvic junction on the left side was somewhat obscured by a band thought to be of vascular nature. At the end of 20 minutes there was a good deal of dye in the bladder and no abnormality of this viscus was noted. Roentgenologically this intravenous pyelogram was interpreted as being compatible with a bilateral pyelonephritis with a possible vascular band at the left ureteral pelvic junction and an atrophic right kidney. Polycystic kidneys could not be ruled out.

In chronological progression an examination of the GU tract was next performed after the retrograde injection of a radio-opaque substance. Both kidneys were well outlined by this method. A small atrophic right kidney was described and a bifid pelvis was present in the left. All of the calices appeared blunted. This was thought to be probably indicative of

infection. There was a slight dilatation of the left ureter and pelvis and to a lesser extent the calices.

Six weeks after admission a small right kidney was freed from moderately dense adhesions and surgically removed.

Gross examination of this kidney including the pelvis revealed that it weighed only 16.5 grams and measured 5 x 2.5 cm. The capsule was

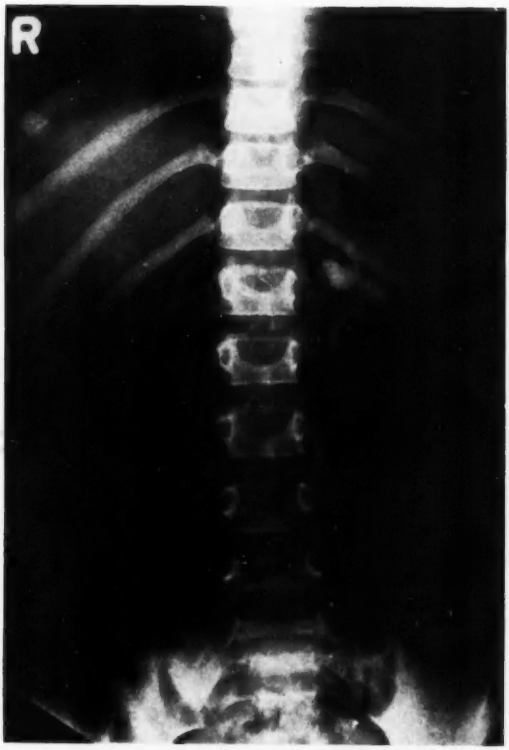

FIG. 1. I.V. Pyelogram. Note atrophic, small right kidney

slightly thickened but could be easily stripped, leaving a smooth, lobular surface which was markedly congested and had a few subcapsular hemorrhages. The pelvis was dilated and measured 2.5 x 1 cm., its wall being thick and fibrous. On section there was a definite diminution in the amount of cortex and the division between cortex and medulla was poorly defined. There was an apparently normal blood supply. There were two

major and four minor calices of fibrous consistency and the renal parenchyma was replaced by fibrous tissue.

Microscopically, sections showed remarkable fibrosis with sclerosis of the blood vessels and glomeruli, many being completely obliterated and the walls of others being greatly thickened. There was extreme distortion of the tubular structure, many tubules containing hyaline material (casts). Diffuse leucocytic infiltrations existed in some areas, plasma cells predominating. The picture was that of chronic pyelonephritic kidney.

The post-operative course was characterized by the rapid disappearance of the presenting symptoms. The amaurosis present on admission was transient and full visual acuity returned within a few days.

The blood pressure recordings were not striking in that there was no immediate lowering of hypertension, but the results were encouraging. Within the first 2 weeks post-nephrectomy the systolic pressures ranged from 170 to 140 and the diastolic from 120 to 100, with a rough average of 150/110. By the end of one month the average was 130/90. Fundoscopic re-examination revealed some residual changes; i.e. a slight papilledema of 1 diopter, a narrowing and tortuosity of the retinal arterioles and a scarring in the macular regions.

A low grade intermittent febrile course characterized the convalescence. During this period a thorough search for foci of infection was carried out and resulted in the extraction of several carious teeth.

Catheterized urine analyses showed a persistent cloudiness, a neutral reaction, a specific gravity between 1.014 and 1.019, with initial post-operative spillage of 120 mgm. of albumin, reduced to 5 mgm. of albumin within 2 weeks. There were many white cells, often in clumps initially, but subsequent urines have been clear of any cells.

The N.P.N. was 22 mgm.%, the urea nitrogen 18.7 mgm.%. Concentration tests, consisting in restricting the water intake for 24 hours and determining the amounts of urine voided at intervals and the specific gravity of each specimen revealed an ability to concentrate up to 1.020. Urine cultures done post-operatively grew out pseudomonas aeruginosa (B. pyocyaneus).

The child was discharged, asymptomatic and in a much improved nutritional state. Activity has been restricted and all precautions taken to guard the patient from acute respiratory disease. An adequate diet was advised. The child has been kept under close observation in the out patient department.

Discussion

Dr. William Howard: The syndrome of malignant hypertension associated with kidney disease is an uncommon occurrence in pediatric practice, but its appearance in this age group presents an unusual challenge in

management. This child illustrated vividly the gradual development of hypertensive symptoms over a 3 year period culminating in convulsions and temporary blindness. The characteristic persistent elevation of blood pressure, high diastolic pressure and low pulse pressure, combined with a hypertensive retinopathy were sufficient to underline the seriousness of the patient's condition. The urologic studies indicated the probability of an etiologic relationship between the small, atrophic, non-functioning right kidney and the malignant hypertension. Based on results obtained in similar cases, extirpation of the diseased kidney was felt to be the most desirable therapeutic procedure. The wisdom of this decision cannot be judged too soon after operation, but present indications are favorable.

Since the time of Richard Bright, it has been suggested that there was a causal relationship between renal disease and certain types of hypertension, and recent studies have served to emphasize and elucidate that association. The classic experiment of Goldblatt amply confirmed by the work of others has shown that renal ischemia is one of the principal factors in the production of hypertension in renal disease. It was shown that the arterial hypertension associated with renal ischemia was due to a pressor substance elaborated by the kidney. This pressor substance, renin, is an enzyme which is liberated into renal vein blood. Here it interacts with pseudoglobulin substrate in blood known as preangiotonin or pre-hypertensin. This latter substance is probably formed by the liver in the presence of an adequate amount of functioning adrenal cortical tissue. The combination of renin and preangiotonin forms the final effector vasoconstrictor and pressor substance, angiotonin.

Schroeder postulates the existence of two conditions which cause renal ischemia: (1) functional, spasmodic constriction of arterioles by nervous or hormonal influences; and (2) structural or organic changes in the renal blood vessels. According to this view, hypertension from any cause, if persisting long enough will result in renal arteriolar sclerosis, thus changing the functional constriction of the arterioles into an organic one.

Advances in the knowledge of the pathogenesis and treatment of pyelonephritis have given added information concerning the hypertension associated with chronic or healed pyelonephritis. Certainly, when considering hypertension of renal origin, chronic pyelonephritis appears to be one of the most important causes. It is estimated that 15 to 20 percent of cases of malignant hypertension are due to pyelonephritis, even though the kidney infection may have run its course, with subsequent healing. It is also one of the most frequently encountered causes in children.

Clinical interest and experimental effort have centered on the unilateral atrophic damaged kidney associated with hypertension in an attempt to effect surgical relief of the elevation of blood pressure. Sufficient reports have accumulated in the literature to indicate the effectiveness of nephrec-

tomy in such cases, but long time follow-ups have revealed that ultimate results are not always satisfactory with regard to permanent lowering of blood pressure. From this accumulated information has come some assistance in establishing indications and contraindications for surgical therapy in the unilateral lesions.

Kittredge and Brown point out that whenever unilateral nephrectomy for malignant hypertension is contemplated, it must be borne in mind that in hypertension of long duration, irreversible vascular changes may have occurred in other arterioles, which may prevent the return of the blood pressure to normal. If such irreversible changes are present, little may be expected from operation. Many authors feel that the duration of hypertension should not exceed two years if operative treatment is to be effective. Patients with malignant hypertension have fared badly after operation unless kidney function has remained near normal. Normal kidney function may be taken as at least one indication of the absence of irreversible blood vessel changes. Patients with a fixed hypertension and relatively few symptoms are also considered poor candidates for operation.

In dealing with children, it is difficult to estimate the length of time necessary for persistent hypertension to produce irreversible changes. Pediatricians are constantly impressed by the recuperative and regenerative powers of the child, and it is never safe to assume that such changes are permanent in the pediatric patient. Simply because of the age factor, the underlying pathology is usually of fairly short duration in childhood. For these reasons it is suggested that the prognosis for the relief of hypertension from unilateral renal disease in children may be exceptionally good as compared to the equivocal results so far obtained in adults.

In the present instance, the blood pressure was persistently high, and was associated with severe symptoms of a rapidly progressive nature. There was no improvement on prolonged bed rest, and the retinopathy became more severe. The child's condition was critical, and little could be expected unless nephrectomy could effect some relief. The long duration of symptoms was an ominous note although the exact duration of the hypertension could not be accurately determined. It could only be hoped that the presence of good kidney function, the absence of azotemia, and the failure to demonstrate any cardiac damage presaged a satisfactory outcome.

The child's postoperative course, while not as dramatic as in the case recently reported by Kennedy, Barker, and Walters, has been rather satisfactory. The blood pressure, after showing a prompt drop to the neighborhood of 155/110, then required several weeks to reach a level of 120/80. This further decrease occurred during a time when the child was allowed full activity about the ward. The hypertensive retinopathy has gradually

regressed, leaving only some scarring in each macular area. The vessels are not normal, and there are no hemorrhages, exudates or choking of the discs. Before this improvement can be considered as permanent and indicative of a cure, the child must be followed for at least two more years, during which time the blood pressure should remain within normal limits.

In spite of the progress to date, one serious problem remains to be settled before we can hope for any permanent good result. The persistent urinary tract infection remains a grave danger to the functional efficiency of the one remaining kidney. X-ray findings after retrograde pyelography indicate that infection has made some changes in the pelvis of the left kidney, which is also a bifid pelvis. If this infection persists subsequent damage to this kidney may nullify the improvement so far observed. Final elimination of this infection appears to be essential to the continued management of this child.

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TETANUS

A Study of 12 Cases Seen at Children's Hospital, Washington, D. C.

Dr. Hubert L. Ried

The purpose of this paper is to review those cases of tetanus which have been admitted to Children's Hospital, from 1940 to 1945 inclusive. During this five year period, 12 cases of tetanus were seen. The greatest incidence of the disease was noted in 1942 when 6 cases were treated; in 1945, 3 cases were treated; and in 1941, 1943 and 1944 one case each year was treated. There were no cases admitted in 1940.

Incidence: Eight of the 12 cases occurred in children 5 years of age. The youngest patient was 3 years of age; the oldest patient was 12 years of age. Males were effected one and one-half times more frequently than females. There was no difference in incidence noted as to race, six of the patients being colored and 6 being white.

Portal of entry and incubation period: It is interesting to note that in two of the cases no portal of entry for the organism could be found even after repeated examination. In the remaining ten cases, various types of injuries were found. Most of these wounds were lacerations received from falls. Other types of wounds included a pitchfork wound, a penetrating wound of the foot caused by a wooden splinter, a rusty screw puncture wound of the foot, and a laceration of the upper lip after a fall in a play yard. The length of the incubation periods varied from 5 to 10 days, the average being 7 days. In this series paradoxically enough the cases in which the incubation was longest had the highest mortality rate. The 2 cases with incubation periods longer than 7 days were fatal. Of those cases with incubation periods of 7 days duration (4 cases) 3 recovered and 1 died. The case in which the incubation period was 6 days in duration was fatal, whereas the case with an incubation period of 5 days recovered. In 2 cases, the incubation period could not be estimated because no site of entry for the organism could be found. In one case, two lesions were present; one of these lacerations had been received three weeks before the onset of symptoms, but appeared well healed; the other lesion had been received one week before admission and was in the process of healing. It is believed that the latter was the lesion that acted as a portal of entry for the tetanus bacillus (see Table I).

Presenting symptoms: The most common presenting symptom was trismus which was present in 50% of the cases. The next most common complaint was stiffness of the neck, back and legs. This was noted in 25% of the cases. In 2 cases the chief complaint was sore throat and difficulty

in swallowing. In these cases, there were no signs of an accompanying pharyngitis or tonsillitis. In one case the presenting symptom was a convulsive seizure. Headache was a common complaint in conjunction with the above presenting symptoms.

Physical Examination: On physical examination most of the patients had nuchal rigidity of some degree. Risus sardonicus was noted in 4 of the 12 patients and definite opisthotonus was seen in 2 cases. Further examination of the patients revealed a slight to marked degree of spasm of the muscles of the lower extremities. Four of the cases, excluding those with opisthotonus, showed moderate spasm of the erector spinae group of muscles. The reflexes were reported as hyperactive in 9 cases. In these 9 cases, a positive Babinski sign was noted 3 times. In the remaining cases, no mention was made of changes in the reflexes.

TABLE I

CASE	PORTAL OF ENTRY	INCUBATION PERIOD	OUTCOME
1	unknown	unknown	recovery
2	small abrasion, left leg	unknown	recovery
3	laceration of left knee	6 days	died
4	puncture of foot (pitchfork)	7 days	died
5	wooden splinter in great toe	9 days	died
6	laceration of upper lip	6 days	died
7	laceration of knee	5 days	recovery
8	laceration of right thigh	approx. 7 days	recovery
9	laceration of left thigh	7 days	recovery
10	unknown	unknown	recovery
11	puncture wound of foot	10 days	died
12	laceration of left ankle	7 days	recovery

Four of the 12 cases presented signs of local inflammation at the site of injury. In these cases, there was a slight amount of purulent drainage from the lesions. In 4 cases no local inflammation was noted and the wound appeared to be healing well. In the remaining cases in which a site of entry could be found, no mention was made of the appearance of the wound on examination.

The temperatures on admission varied from 99.6° to 104.6° rectally, the average temperature being 101.2°. The pulse rate was increased in proportion to the temperature in most cases as was the respiratory rate except in those few cases in which the accessory muscles of respiration were spastic. In these latter cases the respirations were shallow and rapid.

Laboratory: Laboratory work on these patients consisted of blood counts, urinalysis and in some cases lumbar punctures and cultures of the material

from the wounds. The average hemoglobin reading in these cases was ten grams. The leucocyte counts ranged from 7,000 to 13,000 cells per cmm., the average being around 10,000 per cmm.

Urinalyses on all patients were essentially negative. Lumbar punctures were performed in 5 of the 12 cases and were normal in each.

Cultures of material from the wounds were made in 4 of the 12 cases. In 1 case a hemolytic streptococcus and a hemolytic staphylococcus was isolated. In another case, no anaerobic organisms could be cultured. In the third case, culture revealed an anaerobic hemolytic streptococcus and a Gram positive bacillus with subterminal spores. In the fourth case, the tissue excised from the wound was sent to the U. S. Public Health Laboratory which reported a positive culture of Clostridium Tetani from the specimen. Thus the organism causing the disease could only be isolated in 16% of the cases.

Diagnosis: There is usually little difficulty in making a diagnosis of tetanus. Occasionally, however, the diagnosis may be somewhat equivocal. In this series of cases tetanus was recorded as the first diagnostic impression in all the cases. In 2 of the cases (those which presented no wound) the possibility of other disease entities was considered including meningitis, encephalitis and poliomyelitis. Prompt lumbar punctures and development of further pathognomonic signs ruled out these diseases. Other conditions which may at times be confused with early tetanus are tonsillitis, peritonsillar abscess, arthritis of the jaw and rabies. Strychnine poisoning may simulate tetanus very closely. However, in this condition trismus is rare and persistent muscular rigidity is not present between paroxysms of convulsions.

The clinical courses of the patients included in this series were not unusual. In the 7 cases which recovered, the muscular spasm and rigidity gradually subsided under adequate therapy. Convulsions, which at times were severe and extremely difficult to control, became less frequent. In the cases that were fatal, the muscular spasm and rigidity tended to increase, the convulsions became more frequent and severe, and the temperature became elevated until death supervened. The temperature in the non-fatal cases ranged from 99.6° to 103.4° while in the fatal cases the temperature remained at similar levels until terminally when it often rose to 106° to 108°. This is in accord with the general opinion that a rapid rise of temperature fore-ordains a bad prognosis.

Mortality and Length of Hospitalization: The mortality rate in this series of cases was 41.7%. This compares favorably with the results obtained in other large hospitals. Altemeier[1] in his series of 16 cases reports a mortality of 62.5%. In the fatal cases, the duration between the onset of symptoms and the beginning of treatment varied from 4 hours to one day.

The duration of hospitalization in the fatal cases varied from 2 to 6 days, the average being 3 days. In the non-fatal cases the time elapsing between the onset of symptoms and the beginning of treatment was from 3 hours to 5 days, the average being 2 days. The length of hospitalization in these cases averaged from 10 to 14 days.

Complications were infrequent in this series. Serum reactions will be discussed under treatment. In one case a fracture of the clavicle occurred, this resulting when the patient fell out of bed during a convulsive seizure. In one of the fatal cases, atelectasis and bronchopneumonia were diagnosed clinically before death. There were no other complications reported. The postmortem findings were in accordance with the general concept that there are no lesions found that are characteristic of the disease. Goldscheider and Flatau and Nissl have found swelling and fragmentation of the tigroid bodies of the motor ganglion cells and shrinkage with deep staining of the nuclei but this condition is found under many other circumstances and is by no means specific.[2]

Treatment: The patients were placed in darkened rooms and external stimuli eliminated as much as possible. Care was taken to avoid injury during a convulsive seizure. In most instances, an aspirator was available in each room, and oxygen was used freely in those patients exhibiting the slightest respiratory distress.

A thorough debridement of the wound was done in 9 of the 10 cases having a demonstrable wound. The devitalized tissue was removed and adequate drainage of the wound instituted. Following debridement, 10,000 units of antitoxin was infiltrated into the area about the wound. In no case was infiltration about the wound repeated. In one case in which there was a wound of the upper lip no debridement or infiltration with antitoxin was performed. In 3 cases, 10,000 units of penicillin was also infiltrated into the area about the wound. Further treatment of the wounds consisted of local dressings with hydrogen peroxide, boric acid dressings, or sulfonamides.

Tetanus antitoxin was promptly administered parenterally to all patients shortly after admission. Routine sensitivity tests were carried out in all cases and in no instance was it necessary to carry out desensitization measures. The initial dosage of antitoxin varied greatly, ranging from 20,000 to 100,000 units. This dose was given either intravenously or intramuscularly. If given intravenously the initial dose was followed by intramuscular injection of from 20,000 to 60,000 units of antitoxin. After the initial dose additional antitoxin was given in varying amounts depending on the response of the patient. The total dosage varied from 70,000 to 250,000 units. Four of the cases received 70,000 or more units of antitoxin. Of these cases, two died and two recovered. Seven of the cases

received between 100,000 and 200,000 units of antitoxin. Of these cases, 3 died and 4 recovered. One patient received 254,000 units of antitoxin and recovered. The average total dose of tetanus antitoxin used in this series of cases was 125,000 units.

In none of the cases was tetanus antitoxin administered by the intrathecal route. There is at present some controversy over the relative value of antitoxin given by this method. Firor[3] was unable to demonstrate any superiority of the intrathecal mode of administration over the intravenous route. In a later publication, however, Shumaker, Firor and Lamont[4] concluded from experimental work that "if animals are treated early enough with a sufficient dose of antitoxin, all will survive whether treated by the intravenous or intrathecal route; and that conversely, if the treatment is delayed so long that a fatal amount of toxin has been fixed, antitoxin given by either route will be futile." It is well to bear in mind, however, that the intraspinal route is often dangerous because of the excitement induced, the technical difficulties encountered in highly spastic patients, and the possibility of inducing a sterile or septic meningitis in patients already hyperexcitable.[5] On a number of occasions death has been directly attributed to the intracisternal or intraspinal injection of tetanus antitoxin.[6]

In this series one case showed an immediate reaction to the intravenous injection of antitoxin. This reaction manifested itself by severe respiratory distress and was controlled by the subcutaneous injection of 0.5 cc. of adrenalin and the free use of oxygen. No cases of delayed serum reactions were noted.

Sedation of the patients was maintained by the use of paraldehyde. The dosage varied from 3 cc. to 8 cc. depending on age and condition of the patient. In all instances it was given rectally in cottonseed or mineral oil and the initial dosage was repeated every 3 to 6 hours. In some cases sodium phenobarbitol was used to supplement paraldehyde, the dosage varying from $\frac{1}{2}$–$1\frac{1}{2}$ grains every 3 to 6 hours. Chloral hydrate was also used in some of the cases, the average dosage being 5 grains every 3 to 5 hours. In a few cases avertin was used. This was given in doses of 80 milligrams per kilogram of body weight every 6 to 8 hours.

Penicillin was used in 3 of the 12 cases. After debridement, 10,000 units were infiltrated into the area about the wound. The drug was also given by intramuscular injection, the average dose approximating 20,000 units every 2 or 3 hours. In one case, a total of 750,000 units were given over a period of 3 days with the patient recovering. In a second patient, a total of 480,000 units was administered over a period of 3 days; this case ended fatally. In the third patient, a total of 800,000 units was used over a period of 4 days and was then discontinued; however, it was started again

4 days later because of the development of bronchopneumonia. However, the child succumbed. It appeared that the administration of penicillin had no salutary effect on the course of tetanus per se. Its use is indicated when complications such as bronchopneumonia or secondary wound infection occur during the course of the disease. Although the cases of tetanus treated at this hospital with penicillin have been too few to draw any categorical conclusions, the results are in agreement with those obtained by Altemeier[1] who concluded from a series of 16 cases of tetanus treated with penicillin that the use of this drug failed to exert any beneficial effect in uncomplicated cases of the disease. It is well known that penicillin has a bacteriostatic action against Clostridium tetani in vitro. However, the toxin elaborated by the organism produces the untoward effects which characterize the disease. It is therefore understandable why penicillin would have little if any virtue against tetanus.

SUMMARY

Twelve cases of tetanus treated at Children's Hospital, Washington, D. C. from 1940 to 1945 inclusive are reviewed. Eight of the 12 cases occurred in children 5 years of age. The incubation period varied from 5 to 10 days. The patient with an incubation period of 5 days recovered, whereas the patient with an incubation period of 10 days died. This is at variance with the usually encountered instance of a shorter incubation period heralding a more severe prognosis. The most common presenting symptoms in order of the frequency were: trismus, stiffness of the neck, legs and back, sore throat and difficulty in swallowing and convulsions. Headache was a common accompanying complaint. Laboratory work including complete blood counts, urinalyses, and spinal fluid examinations were essentially negative. In 2 cases, Clostridium tetani was isolated. Postmortem examinations revealed no specific lesions. The mortality rate was 41.7%. Complications consisted of a fracture of the clavicle, and in one case, a terminal bronchopneumonia and atelectasis.

Treatment consisted of isolation in a quiet darkened room, tetanus antitoxin in total doses varying from 70,000 to 245,000 units, sedation with paraldehyde, chloral hydrate, phenobarbital, or avertin. Penicillin was used in 3 uncomplicated cases of tetanus with no apparent beneficial results.

Tetanus is still seen occasionally in spite of widespread prophylaxis. The treatment remains relatively unsatisfactory and the mortality rate is high in the disease. Proper therapy depends upon the neutralization of the toxin before it becomes fixed in the nervous system. Tetanus antitoxin is the only agent which is effective in the neutralization of the toxin of the tetanus bacillus. Further therapy consists of sedation to prevent convulsive seizures, chemotherapy in cases complicated by susceptible infections and good symptomatic and supportive measures.

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ERYTHROBLASTOSIS FETALIS IN A PRIMIPARA

Case Report No. 80

Dr. Clifford J. Tichenor D. P.—46–7665

A two day old white male was admitted to Children's Hospital because of marked jaundice and lethargy.

The past history revealed that the infant had been delivered by Caesarian section 2 weeks before term and was the first pregnancy of an Rh negative primipara. The father was Rh positive. One week prior to section, a routine anti-Rh titer on the mother's serum had showed a level of 1:128 (a considerably elevated agglutination titer—this in spite of primiparity). In going into the mother's history, it was found that she received 3 transfusions 3 years ago (presumably Rh positive blood), thereby sensitizing her to Rh agglutinins.

At the time of delivery 2 days prior to admission the infant was in critical condition. Respirations were rapid and shallow and numerous coarse rales had been audible throughout both lung fields. The cry was poor, and peripheral cyanosis was noticeable. He was markedly lethargic and flaccid with an absent Moro reflex. The pulse was slow (100) and thready. The spleen was palpably enlarged 2 cm. below the left costal margin and the liver could be felt one centimeter below the right costal margin. There was noticeable pallor of the mucus membranes postpartem with marked icterus appearing 6 hours later.

A hemogram at birth showed the red blood cells to be 2,260,000 with 79% hemoglobin. There were 209 erythroblasts per 100 white blood cells and 45,700 white blood cells. An immediate transfusion of 75 cc. Rh negative type O blood was administered with noticeable improvement during the next 6 hours. A hemogram the following morning showed 2,870,000 red blood cells with 83% hemoglobin. A second transfusion of 40 cc. Rh negative type O blood was given the day before admission.

During the first hospital week the hemoglobin maintained itself moderately well. The infant remained rather lethargic and took its feedings only with urging. The cry was fair and the Moro reflex was sluggish. The jaundice continued to be marked and the spleen and liver remained palpably enlarged. At this stage the lethargy was thought to be due to the jaundice (a frequent concomitant feature of jaundice due to any cause is apathy) but it was considered that it might have represented a central nervous system involvement due to kernicterus.

Sixty cc. of Rh negative blood was given on the ninth day and 80 cc. of Rh negative blood was administered 4 days later. By the tenth day,

the jaundice was subsiding to some extent but the infant remained apathetic and continued to take his feedings rather poorly. By the 17th day the infant appeared much improved. He was much more active and had a vigorous cry. The Moro reflex was now normal and there was considerable more tonicity to the extremities; the latter had been moderately flaccid at the time of entry. It had been necessary to gavage half of the feedings,

TABLE I

DATE	RBC	Hb	WBC	ERYTHRO-BLASTS	COMMENT
8/17/46	2,260,000	12.5	45,000	209	75 cc. transfusion Rh negative type O blood
8/18/46	2,870,000	13			40 cc. Rh negative type O blood
8/19/46	3,600,000	13		32	
8/20/46	5,460,000	14			
8/22/46	4,300,000	14.5	18,600		
8/23/46	3,730,000	12.5			
8/24/46	4,250,000	12			
8/27/46	4,030,000	12.5			
8/28/46	3,320,000	12	15,000		55 cc. transfusion Rh negative type O blood
8/29/46	3,500,000	12	9,200		80 cc. transfusion Rh negative type O blood
8/31/46	7,050,000	14			
9/ 3/46	3,580,000	12.5			
9/ 4/46	3,760,000	12	23,500		Rh negative with 87% anti-Rh sera
9/ 7/46	3,390,000	11			
9/10/46	3,080,000	10.5			35 cc. transfusion Rh negative type O blood
9/12/46	Coagulation time 3 minutes				
9/13/46	3,530,000	11.5			
9/14/46	3,060,000	9.5	Bleeding time less than 1 minute		70 cc. transfusion Rh negative type O blood
9/16/46	3,850,000	10.5	22,300		
9/17/46	3,780,000	12			
9/31/46	3,500,000	11			Rh negative with 87% anti-Rh sera
10/17/46	3,400,000	10			Rh positive with 87% anti-Rh sera

but the extent of the infant's vigor now permitted him to take all feedings from the bottle. The jaundice was still subsiding and the hemoglobin maintained itself at 12.5 gms. The patient received 6 transfusions of Rh negative blood in all or a total of 350 cc. Table I illustrates the pertinent laboratory data.

Follow-up examinations after discharge revealed no overt neurological sequellae referable to a possible kernicterus and the infant has shown con-

stant improvement in his nutritional status. An interesting sidelight was that the infant temporarily remained Rh negative for a full month following receipt of the last Rh negative transfusion.

Discussion

Dr. John Cassidy: This case report illustrates rather well what may occur when a female is transfused with blood without proper attention being paid to the Rh group. In this particular instance when the mother was transfused, Rh grouping was not performed as a routine procedure.

It is an established fact that iso-immunization by the Rh factor may occur in at least 2 ways, namely, by repeated transfusions of Rh positive blood in Rh negative individuals, and by Rh positive fetal blood in pregnant Rh negative women.

Repeated observations and reports have shown that one or more pregnancies with Rh positive infants are required to induce a sufficient degree of iso-immunization to produce an infant with hemolytic disease of the newborn. Once an Rh negative woman is immunized, each successive pregnancy with an Rh positive fetus results in increasingly severe forms of this disease.

It is logical then that hemolytic disease of the newborn occurs only rarely in the first born, and in those instances when it does occur, one should be highly suspicious that an Rh negative mother some time in her life had been transfused with Rh positive blood. Levine and Waller[1] in a recent report undertook to investigate this phase and their studies in instances of the disease in the first born show definitely that there is usually some previous instance in the mother's history where she has been immunized by transfusions of Rh positive blood. In those instances where the mother has received previous transfusions, the disease in the first born is usually of the severe type and often results in the death of the infant.

It is well for us who are constantly treating children to remember that we have a definite responsibility with regard to transfusions for girls in the pediatric age group. While it is true that the time interval between the child bearing age and the time we see them is usually considerable, nevertheless transfusion of an Rh negative female child with Rh positive blood is apt to produce iso-immunization. And once an Rh negative girl is immunized, she must be considered as remaining potentially immunized for the remainder of her lifetime.[2]

It is most likely that in the case reported if the mother had not received the transfusions, or if she had been transfused with Rh negative blood instead of random blood, the first pregnancy would have resulted in an infant free of the disease, and likewise for the next pregnancy. The obstetrical future for this mother is not too bright unless her mate is a heterozygous Rh positive, thus capable of producing an Rh negative fetus.

In our records here at Children's Hospital there are 2 other instances of isoimmunization in females induced by transfusions of Rh positive blood in which the first born showed evidence of hemolytic disease. In one of these the infant had the most severe form, hydrops fetalis, and did not survive. These cases are reported in detail in a previous issue of the Clinical Proceeding.[3]

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TYPHOID FEVER

A Report of 35 Cases at Children's Hospital from 1939–1944

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Stephen Jones, M.D.
John Kelly, M.D.

This paper is presented as a resumé of 35 cases of Typhoid fever seen during the six year period from 1939–1944 at Children's Hospital.

Typhoid fever is world-wide but is especially prevalent in the tropics and sub-tropics where foreigners are more susceptible than the natives. In fact the Chinese are highly immune due to previous abortive infections in childhood. There is no racial or sexual prevalence and all ages seem to be equally susceptible except in the infant age group. It was formerly thought that infants were immune but in our series there were 2 cases under one year of age and 8 cases under two years; Sako and Fleet recently reported a typical case in an infant 7 months old. It is possible that the apparent rarity of Typhoid in infants is due to lack of exposure and not to any natural or congenital immunity. However, it must be noted that in the more rural sections where prophylaxis is almost entirely absent, there is still a very low incidence in the infant age group. It may be mentioned that Typhoid bacillus "H" agglutinins (though no "O" agglutinins) may be found in the newborn infant's blood if they are present in that of the mother.

Although Typhoid is relatively rare in the north there are several classical epidemics noted in the literature. The one at Wesleyan College in Connecticut in 1894 which was traced to oysters that had been contaminated by infected sewerage is an example. In the temperate zones it almost always appears in small isolated epidemics traced to a single source, frequently a carrier from a more southern locality or the residual of a previous epidemic.

In reviewing this series of cases it is of some interest to note how frequently this disease was diagnosed on admission from the clinical picture and the history alone. Eight of our cases were definitely considered to be Typhoid before any laboratory confirmation was obtained and in 9 more cases Typhoid was thought to be the probable diagnosis. This is of some importance in view of the fact that in localities where Typhoid is prevalent, laboratory facilities are frequently unavailable and one often must depend on a clinical impression. These clinical impressions were based on (1) the history with special reference to contacts such as water supply and environment, (2) the onset, the season and accompanying symptoms and

(3) the physical examination which may show prostration, high temperature, tender distended abdomen, splenomegaly and often rose spots later on.

TABLE I

Summary of 35 cases of typhoid fever

PATIENT	AGE	RACE	SEASON	KNOWN CONTACT	LEUCOPENIA	POSITIVE BLOOD CULTURE	POSITIVE STOOL CULTURE	WIDAL		DURATION	COMPLICATIONS
								"O"	"H"		
										days	
1	4	C	Sum.	0	0	+	+	1:640	1:320	37	0
2	3	C	Sum.	0	+	+	0	1:640	1:640	35	0
3	8	C	Fall	+	+	0	+	1:640	1:640	40	0
4	3	W	W	0	0	0	0	1:200	1:200	28	0
5	3	W	Fall	0	+	+	0	1:40	1:40	40	0
6	10 m	C	Fall	+	0	0	+	1:320	1:80	35	0
7	6	W	Sum.	+	+	0	0	1:200	1:200	14	0
8	1	W	W	0	0	0	+	1:320	1:160	8	0
9	6	W	Spr.	+	+	+	+	1:160	1:160	38	0
10	9	C	Fall	+	+	+	0	1:100	1:100	30	0
11	5	C	Sum.	0	0	+	+	1:160	1:20	30	0
12	6	C	Fall	+	+	+	0	1:640	1:640	30	+
13*	7	C	W	0	+	+	0	1:320	1:80	38	0
14	19 m	C	Sum.	0	+	+	+	1:180	1:180	28	0
15	11	W	Fall	+	0	0	0	1:400	1:100	12	0
16	4	W	Sum.	+	+	0	+	1:320	1:150	20	0
17	18 m	W	Fall	+	+	+	+	0	0	30	0
18	17 m	C	Sum.	0	+	+	+	1:640	1:640	30	0
19	6	C	W	+	0	0	+	1:800	1:800	34	0
20	3	C	Spr.	0	0	+	0	1:320	1:320	36	0
21	3	W	Sum.	+	0	+	+	1:80	1:80	4	0
22	3	W	Sum.	+	0	+	+	1:800	1:800	37	0
23	20 m	W	Sum.	+	0	+	+	0	0	25	0
24	8	W	Sum.	0	0	0	0	1:160	1:20	35	0
25	14	W	Spr.	0	+	0	+	1:640	1:240	30	0
26	3	W	W	+	0	0	0	1:100	1:25	8	+
27	12	W	Spr.	+	+	+	+	1:640	1:640	53	0
28	4	C	Fall	+	0	0	+	1:640	1:80	25	0
29	5	W	Sum.	+	+	0	0	1:800	1:400	20	0
30	2	C	W	0	+	0	0	1:128	1:320	21	0
31	8	W	Sum.	+	+	0	0	1:160	1:160	21	+
32	3	C	Sum.	+	+	+	+	1:320	1:160	30	0
33	21 m	W	Fall	+	+	0	+	1:320	1:320	18	0
34	2	W	Sum.	+	0	0	+	1:320	1:320	16	0
35	5	W	W	0	+	+	+	1:8003	1:320	50	

* Vaccinated 3 yrs. previously.

At this point it should be noted that the clinical picture depends on the stage of illness when the patient is first seen.

To elaborate further on the above mentioned points we will briefly discuss them in relation to our findings and those of current reports.

(1) *The History of Contact* (positive in over 60% of our cases). Typhoid should be thought of when a case is admitted from the rural districts or where the patient has been visiting these areas and drinking well water or has had contact with a known carrier. Three of our cases had been in contact with known carriers. It is probable that on closer interrogation similar histories could have been obtained from our other cases.

(2) *The Season*. The disease is seen in every month of the year but has its peak incidence in the late summer or fall often with a secondary peak in the winter in case of epidemics. More than two thirds of our cases were seen in the summer and fall.

(3) *Signs and Symptoms*. Headache and anorexia were part of the presenting picture in approximately 75% of our cases. The commonly accepted physical findings which are usually listed as criteria of Typhoid fever include high sustained fever with a low temperature-pulse ratio, splenomegaly, rose spots, gastro-intestinal signs such as tenderness and distention and the typhic tongue.

As regard these findings our cases were not too typical. Only 4 of our patients presented the plateau type of temperature curve which is supposedly characteristic of Typhoid fever. In children the temperature curve is often atypical and maintains a relatively high spiking course for the first 10 days and then gradually returns to normal by lysis during the following 10 days. The dicrotic pulse is unfrequently seen in children and we had only 5 cases which presented this finding and these were all over 6 years of age.

As for the enlargement of the spleen which is usually noticed by the tenth day of illness, we had a 20% incidence which is a little below the average.

The typical maculo-papular rose spots usually appear by the tenth day in successive crops and disappear on pressure. They are found on the trunk in most of the cases and usually first appear just beneath the lower left costal margin and above the umbilicus. In only 6 cases in our series was a typical rash noted and all these were white children. The difficulty of discerning these spots in a negro child is apparent. Rose spots rarely last more than 3 days and hence unless a thorough physical examination is done at least every other day they are likely to be overlooked. One exception to this was case #27 who showed successive crops of rose spots for over 2 weeks. The abdominal distension and tenderness were observed in about 50% of our cases.

The average mortality of Typhoid in children is about 2.2% according to Brenneman while the United States Census Bureau in 1940 reports a mortality rate of 9% in infants under one year. Our death rate was zero

and there were no complications other than 4 cases of bronchopneumonia. The average length of hospitalization was 28 days.

LABORATORY DIAGNOSIS

The 4 laboratory aids which are helpful in confirming the diagnosis include blood culture, stool culture, serology and the white-cell count.

Brenneman states that 75–90% show a positive blood culture in the first week of the disease. In our series positive cultures were obtained in 50% of the cases. If a positive culture is not found during the first week, it is likely that the organism will not be isolated from the blood subsequently.

The stool culture usually becomes positive in the second week and remains positive for about 2 weeks thereafter. A positive stool culture together with a characteristic clinical picture is diagnostic; without the latter, one must think of the possibility of the carrier state. Stool cultures were positive in 21 of our cases (60%). It may be mentioned that the urine cultures for Typhoid are positive in 20% of cases; however, no urine cultures were done in our group of cases.

The agglutination tests depend on the development of antibodies in the blood and the agglutination of a known antigen by these antibodies. The commonest and most widely accepted test is the Widal method. There are 3 agglutinogens in a Typhoid bacillus; the "H" or flagella factor which is frequently produced by immunization; the "O" factor which is usually the result of active infection with living organisms; the third factor, a more recent discovery but of equal importance, is the "Vi" or virulence antigen. The "O" and "H" factors require about 10 days to form immune bodies in the serum; hence agglutination tests usually appear positive on or after the tenth day and often remain positive for many years. As previously noted, a high "O" titer is considerably more significant diagnostically since the "H" factor can be elevated by immunization. The "Vi" antigen-antibody which also appears in the blood by the tenth day may be considered a criterion of the virulence of the organism. If there is a rapid rise in the "Vi" reaction early in the disease one can predict a rapid and satisfactory recovery since it indicates a quick response of the individual's immune defenses. On the other hand a sharp rise in the "O" titer may be of bad import because it indicates a more active infection.

In our series we had positive agglutination tests for "O" in 32 cases and for "H" in 25 cases. Positive blood and stool cultures in the other cases confirmed the diagnosis without the aid of serology. In a patient presenting the clinical picture of Typhoid but with negative blood and stool cultures a positive Widal is not pathognomonic of Typhoid because of the possibility of a previous innoculation, but in such a case repeated serology tests showing especially a rising "O" titer is of sufficient significance to warrant a positive diagnosis.

Lastly one may mention the presence of leucopenia with a relative lymphocytosis which is particularly characteristic though not pathognomonic of Typhoid in adults. Only 60% of our cases showed a leucopenia suggesting that a low white cell count is less characteristic of the disease in children than in adults.

Prevention of Typhoid is primarily by prophylaxis in endemic areas with TAB or at present TABC (Felix) vaccine containing 1,000,000 killed Typhoid organisms/cc. and 750,000 of each of the paratyphoid group. It is given in 3 doses of .5 cc., 1 cc. and 1 cc. in 3 successive weeks with booster doses every six months or every year. One of our cases was alleged to have been innoculated 3 years prior to the infection but this was not verified.

TREATMENT

The treatment in this series was largely supportive. In general we tried to maintain nutrition with a high caloric soft diet and adequate fluids.

The newer methods of therapy are worthy of mention. Manson-Bahr and others in England have advocated the immediate subcutaneous injections of 25 cc. of "Vi" or Felix antiserum and have claimed rather favorable results. Hodgson of the Lister Institute in England states that combined "Vi" and "O" anti-sera is preferable because the "Vi" antibody stops the multiplication of the organism and the "O" combats the endotoxin.

Waksman has found that Streptomycin is quite effective in vitro but the results in vivo have not been satisfactory. Other workers in this country and in South America have obtained favorable results with bacteriophage and in several South American countries bacteriophage is being used extensively. The efficacy of phage therapy, however, is still too early to evaluate adequately.

CONCLUSIONS

(1) Thirty-five cases of Typhoid fever in Children's Hospital from 1939–1944 are reviewed.

(2) Most of the cases occurred between the years of 2 and 8 with 2 cases under one year.

(3) The possibility of diagnosing Typhoid fever clinically is emphasized.

(4) The laboratory aids used to confirm the diagnosis included blood and stool cultures and the Widal agglutination test. The incidence of positivity of these tests was 91% for the Widal reaction and 60% and 51% for stool and blood cultures respectively.

(5) The mortality rate in this series was zero and no serious complications were encountered.